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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,570	05/23/2000	Francois Arminjon	MBHIB00-210	9141

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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,570	ARMINJON ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,22,24-27 and 29-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,24-27 and 29-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed June 13, 2006 is acknowledged and entered. Claims 21, 22, 24-27 and 29-45 are pending and under examination.

Claim Rejections - 35 USC § 103

Claims 21, 22, 24-27 and 29-45 are rejected under 35 U.S.C. 103(a) as obvious over Petre *et al.* (WO 93/24148 A1) in view of Arminjon *et al.* (AU 708777 or WO96/37222).

The claims are drawn to a method for preparing a stabilized multi-component vaccine. The components include diphtheria, tetanus, pertussis (toxoid and filamentous hemagglutinin), hepatitis B surface antigen (HBsAg), IPV (inactivated polio virus), a conjugate carrier molecule selected from tetanus and diphtheria toxoid and a capsular polysaccharide of HiB (*H. influenzae* type B), and an aluminum salt. Specifically, the tetanus toxoid and diphtheria toxoid are adsorbed onto the aluminum salt before being mixed with the other components, and the conjugate is prepared in a phosphate buffer solution before being mixed with the other components, and wherein IPV is mixed with the other components without being adsorbed onto the aluminum salt. Other claim limitations are of record.

Petre teaches multicomponent vaccines for infants comprising various antigens such as diphtheria, tetanus, pertussis (toxoid and filamentous hemagglutinin), hepatitis B surface antigen (HBsAg), IPV (inactivated polio virus) and HiB (*H. influenzae* type B), (abstract, and page 4, lines 10-36). Petre teaches that the components of the combined vaccine are adsorbed to AH (aluminum hydroxide) or AP (aluminum phosphate). The following excerpt is taken from Petre, "After allowing time for complete and stable adsorption of the respective components, the

different components are combined under appropriate conditions", page 9, lines 1-3 of Petre. Therefore, Petre clearly teaches adsorption prior to mixing with other components.

With particular regard to IPV (inactivated polio virus) which is not adsorbed in the instant claim 23, Petre discloses instances where only one of the components of the multivalent vaccine is adsorbed to an aluminum salt (claim 27) and the other components are not treated. Given the teachings of Petre, one of ordinary skill would have recognized that any components of the multivalent vaccine could be adsorbed, depending on the stability required/desired for each component. This is demonstrated by the fact that Petre teaches that other antigens (besides HBsAg) can be adsorbed or not adsorbed onto aluminum salt (claims 6, 7 and 27).

Petre also teaches amounts of antigens to be used in a 0.5 ml dose of a bulk vaccine, which can be optionally amended to use higher or lower quantities of the active ingredients: 10 Tg HBsAg, 25 Lf diphtheria, 10 Lf tetanus, 25 Tg of inactivated pertussis toxin, and 25 Tg filamentous hemagglutinin (FHA), (page 11-12, examples 3 and 4).

Petre differs from the claimed invention by not reciting the specific types of inactivated poliovirus antigens, types 1-3 (instant claims 33-35), although Petre does teach the use of inactivated poliovirus. Petre also differs from the claims invention by not reciting all of the amounts of antigenic elements of the instantly claimed vaccine (instant claims 33-35). The amounts of antigens in the claimed combined vaccine are: 30 Lf diphtheria, between 20-50 D antigen units of poliovirus type 1, between 4-10 D antigen units of poliovirus type 2, between 8-40 antigen units of poliovirus type 3, 10 Tg HiB, 5 Tg HBsAg, 20 Tmoles of phosphates, 5 Tmoles of carbonates, 0.125 ml of 50 Tmolar tris buffer, and 0.356 mg aluminum salt.

However, Arminjon teaches a stable, multi-component vaccine comprising 10 Tg of PRP-T (10 Tg of HiB conjugated to tetanus toxoid), 1 vaccinating dose of diphtheria, 1 vaccinating dose of tetanus, 15 Tmoles of phosphates or 20 Tmoles of carbonates, 0.25-0.3 mg of aluminum hydroxide, 40 U of polio antigen type I, 8 U of polio antigen type II, 32 U of polio antigen type III, 25 Tg of pertussis anatoxin, 25 Tg pertussis FHA, and 0.125 ml of 50 Tmolar tris buffer (pages 2-3, and examples 12 and 13). Arminjon discusses the immunogenic instability of HiB (also referred to as PRP) coupled to tetanus anatoxin. (Note: Tetanus anatoxin is synonymous with tetanus toxoid. PRP-T is an abbreviation for HiB coupled to tetanus toxoid). Arminjon teaches that the PRP-T should be suspended in a solution containing anions (phosphate or citrate) prior to contacting them with aluminum complexes (page 6, lines 33-40). It would have been obvious to combine the teachings of Arminjon including polio virus antigens types 1-3, the specific amounts of antigens, and the amounts of phosphates, carbonates and aluminum salt from the teachings of Arminjon, with Petre's combined vaccine that comprises the antigenic elements of the claimed invention to arrive at the claimed invention. One would have been motivated to incorporate the teachings of Arminjon into Petre's vaccine because both references teach multi-component vaccine comprising antigens adsorbed to aluminum salts for stability purposes. Although Petre fails to teach the poliovirus antigens types 1-3 and the specific amounts of antigens of the instant invention, one would have been motivated to incorporate the antigens from Arminjon into Petre's method because Arminjon's vaccine demonstrates that multi-component vaccines having antigens adsorbed to aluminum salts are stable and effective for immunization. One would have had a reasonable expectation of success that the antigens of

Arminjon would have been successfully incorporated into Petre's vaccine because multi-component stable vaccines are known, as evidenced by Petre and Arminjon.

The Office has considered Applicant's asserted unexpected results, namely, the seroprotective level of Hib antibody that is exhibited when administered a vaccine with numerous valancies. The unexpected results are directed to a particular level of antibody titer against a particular antigen. Because the combination of the Petre and Arminjon reference has a reasonable expectation of success, one would have achieved the same results that Applicant achieved. Had Applicant established that the combined vaccine would not have worked to stimulate an immune response or induce protection, the obviousness rejection would not stand. However, Applicant has failed to establish that one would expect the combined vaccine of Petre and Arminjon to fail. Therefore, the unexpected results of Applicant's vaccine would have been achieved by one of ordinary skill in the art because it would have been obvious to combine the teachings of Petre with Arminjon.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that the prior art does not provide a particularized suggestion or motivation to make the claimed invention. Applicant notes that with regard to claims 21, 22, 24-27, and 29-45, the Office has failed to identify wherein the cited art there is a suggestion to combine all the antigens recited in the present claims into a single composition in the manner described in the claims. Applicant asserts that the Office has not pointed to teachings in Petre or Arminjon that disclose all of the antigens recited in

claim 21. Applicant asserts that Petre's disclosure on page 4, lines 10-36, only discloses various sub-combinations of antigens, but not all of the antigens in combination.

- In response to Applicant's arguments, the Office has pointed to the teachings of Petre and Arminjon that disclose all of the antigens listed in claim 21. No one reference discloses all of the antigens of claim 21, thus the obviousness rejection.
- On page 4, lines 10-36 of Petre, stable combination vaccines are disclosed. The antigens in the claimed combination vaccines include pertussis toxoid and filamentous hemagglutinin in purified form, tetanus toxoid, diphtheria toxoid, inactivated polio virus, a conjugate of a carrier molecule selected from tetanus toxoid and diphtheria toxoid and a capsular polysaccharide of Haemophilus influenzae type B. The antigens taught by Petre in the combination vaccines include pertussis, tetanus, diphtheria, inactivated polio, and Hib (see page 4, line 24).
- In Example 12 of Arminjon, the combination vaccine comprises the antigens PRP-T (Hib), purified tetanus anatoxin (PTA), purified diphtheria anatoxin (PDA), pertussis anatoxin, pertussis filamentous hemagglutinin (F-HA) and polio antigens (type I-III).
- The motivation to combine or substitute antigens form either Petre or Arminjon comes from the concept of combination vaccines taught by both Petre and Arminjon (see entire disclosures for this concept). Since both references use multiple combinations of antigens that alter in one or more antigens, it would have been obvious to make a combination of antigens that includes those

described by Petre and Arminjon. Arminjon discloses a combination vaccine having all of the antigens of claim 21 with the exception that the polio antigens are not inactivated polio vaccine. Petre discloses a combination vaccine that uses inactivated polio vaccine. It would have been obvious to substitute the inactivated polio vaccine for the polio antigens in Arminjon's combination vaccine. One would have been motivated to do this because both Petre and Arminjon are attempting to prevent polio (Petre, page 1, line 23, and Arminjon, claim 6). Since both are vaccinating against polio, and both use a polio immunogen, it would have been obvious to substitute one for the other.

- Applicant argues that with regard to claim 45, Petre discloses that all components of the vaccine composition are adsorbed onto a suitable adjuvant. Although the Office has pointed to Petre, claim 27, as evidence that not all of the antigenic components need be adsorbed onto an adjuvant, Applicant asserts that claim 27 is specific to the HBsAg antigen in the claimed composition. For the same reason, claims 6 and 7 do not encompass embodiments wherein the antigens are not adsorbed to an adjuvant.
    - In response to Applicant's argument, the Office has considered the claims in Petre and the Petre reference as a whole. The Office agrees that in most embodiments, Petre discloses that the antigens are adsorbed to an adjuvant. However, the claims of Petre are broad and are thus interpreted as such. For example, claim 3 is drawn to a vaccine composition comprising HBsAg and a number of other antigens in combination with an adjuvant (not necessarily adsorbed to the antigens, just in combination), wherein at least one of the other antigens is adsorbed to aluminum

phosphate. Claim 4 is drawn to a vaccine composition comprising HBsAg and a number of other antigens in combination with an adjuvant, wherein at least one of the other antigens is adsorbed to aluminum hydroxide. These claims are reasonably interpreted to encompass antigens that are not adsorbed to any adjuvant. Further claim 7 is drawn to a stable and effective combined vaccine composition directed to the prevention of more than two diseases comprising HBsAg and at least two other antigens. There is no mention of being adsorbed to an adjuvant.

- Applicant argues that the cited art does not imbue the ordinary artisan with a reasonable expectation of success. Applicant points to Eskola et al. (J. Infectious Diseases, 1996, 174:S302-5), Eskola et al. (The Lancet, 1996, 348:1688), and Bell et al., all of record (Vaccine, 1998, 16:637). Each is discussed in turn.
  - Eskola et al. (J. Infectious Diseases, 1996, 174:S302-5) discusses aspects of combination vaccine design, with regard to interference between antigens such as DTPw-Hib.
  - Eskola et al. (The Lancet, 1996, 348:1688) reports that the mixture of DTaP, IPV and Hib interferes with the primary antibody response to poliovirus antigens and Hib in particular.
  - Bell et al. (Vaccine, 1998, 16:637) discloses a decreased in Hib antibody titers in response to a combination vaccine of DPT-a absorbed with aluminum hydroxide and mixed with PRP-T. Applicant notes that Bell reported Hib antibody titer of less than 1, whereas the present specification reports 1.46. Applicant also notes

that the instantly claimed vaccine is capable of inducing the same level of Hib seroprotection as that of Bell which had to be administered three times.

- Applicant also points to WO 99/48525, page 2, lines 3-14, which discusses the interference issue between DTPa and Hib. The WIPO disclosure demonstrates a decreased antibody titer to Hib when combined with DTPa.

In response to Applicant's arguments, the Office has considered each of the references carefully. The concept of interference between antigens, particularly DTPa and Hib is apparent from the references of record. The Office does not dispute that there is potential interference between antigens when combining them together. The issue in this case is whether one of ordinary skill in the art would have had a reasonable expectation of success when combining the teachings of Petre and Arminjon. Given that none of the cited references discloses a complete failure of the combined DTPa and Hib to induce an immune response against Hib, one of ordinary skill in the art would have had a *reasonable* expectation of success. The law only requires a reasonable expectation of success. While Applicant has provided evidence that there may be problems of interference when combining DTPa and Hib, there is no teaching that predicts the utter failure of such a combination. With regard to Applicant's assertion that the instant invention induces a better antibody response to Hib than that disclosed in Bell, the claims do not recite a limitation about the degree of antibody titer induced in one dose. Applicant is arguing a limitation that is not present in the claims. Therefore, the claims remain rejected as obvious of the prior art of record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 8/17/06

STACY B. CHEN
PRIMARY EXAMINER